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What future role might N-acetyl-cysteine have in the treatment of Obsessive Compulsive Spectrum disorders? A systematic review.

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Corresponding Author:	Louise Smith, MSc King's College London London, Europe UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	King's College London
Corresponding Author's Secondary Institution:	
First Author:	Louise Smith, MSc
First Author Secondary Information:	
Order of Authors:	Louise Smith, MSc
	Derek Tracy, MB BCh BAO MSc MRCPsych
	Giovanni Giaroli, MD MSc
Order of Authors Secondary Information:	
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Abstract:	Licensed pharmacological treatments for obsessive-compulsive disorders include SSRIs and tri-cyclic antidepressants. However, a large proportion of patients show minimal or no therapeutic response to these treatments. Recently the glutamatergic system has been implicated in the aetiology of obsessive-compulsive spectrum disorders. It has been postulated that n-acetyl-cysteine could have a therapeutic effect on obsessive-compulsive spectrum disorders through its actions on the glutamatergic system and the reduction of oxidative stress. A systematic review was conducted on the existing literature regarding the efficacy of n-acetyl-cysteine on obsessive-compulsive spectrum disorders, primarily investigating adult cohorts with a secondary aim to investigate child cohorts. Ten studies investigated the effects of n-acetyl-cysteine on obsessive-compulsive disorder, trichotillomania, excoriation disorder and onychophagia. Results cautiously point towards the efficacy of n-acetyl-cysteine as a treatment for obsessive-compulsive spectrum disorders; however there is a dearth of randomised control trials in this area and more research into the therapeutic effects of n-acetyl-cysteine on obsessive-compulsive spectrum disorders needs to be carried out before a firm conclusion can be drawn.
Suggested Reviewers:	Jon Grant University of Chicago jongrant@uchicago.edu
	Sam Chamberlain University of Cambridge srchamb@gmail.com
	Christopher Pittenger Yale University School of Medicine christopher.pittenger@yale.edu

What future role might N-acetyl-cysteine have in the treatment of Obsessive Compulsive Spectrum disorders? A systematic review.

Louise Smith¹, Derek K Tracy^{1,2}, Giovanni Giaroli³

Author affiliations:

¹Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

²Oxleas NHS Foundation Trust, London, UK.

³Department of Psychiatry, University College London, UK.

Author highest academic degrees:

¹MSc

²MRCPPsych

³MD

Corresponding author: Louise Smith

louise.e.smith@kcl.ac.uk

Institute of Psychiatry, Psychology & Neuroscience

King's College London

16 De Crespigny Park

London SE5 8AF

Telephone number: 0207 848 0023

Fax number: 0207 848 0976

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INTRODUCTION

Obsessive-Compulsive Spectrum (OCS) disorders are characterised by persistent intrusive thoughts (obsessions), causing anxiety and repetitive behaviours (compulsions) [1], with behaviours usually directed towards assuaging anxiety [2]. Typically, in the case of obsessive compulsive disorder (OCD), which is the most common and best delineated of the OCS disorders, the individual will have good insight into the fact that their levels of worry and distress associated with their obsessions and compulsions are outside the normal range, and considerably disproportionate, but they nevertheless remain compelled to complete the repetitive behaviours, with undue worry about unrealistic consequences should they fail to do so [3]. Obsessive-compulsive disorder (OCD) affects an estimated 1.6-2.3% of the adult population [4, 5] and 0.25-3% in child and adolescent populations (aged 5-15) [6, 7] with a total cost estimate of \$10.6 billion for the annual direct and indirect costs in the US alone [8].

The broad category of OCS disorders comprises a wide range of conditions, with the classification systems of ICD-10 [9] and DSM-5 [1] somewhat differentially delineating them. Up until recently, the Diagnostic and Statistical Manual (DSM) classified OCD under the wider category of anxiety disorders (DSM-IV; [10], but it has now been reclassified in DSM-5 with its own chapter 'Obsessive-compulsive and related disorders' [1].

Within this chapter are included OCD; body dysmorphic disorder; hoarding disorder; trichotillomania (TTM; hair-pulling disorder); excoriation (skin-picking) disorder; substance/medication-induced obsessive-compulsive and related disorder; obsessive-compulsive and related disorder due to another medical condition; and some other less-specific conditions. Other psychiatric disorders which include an aspect of impulse dysregulation such as bulimia nervosa, bipolar disorder, schizophrenia substance misuse and

pathological gambling are sometimes likened to OCS disorders due to the highly valued and repetitive nature of thoughts and behaviours. The fact that pathological gambling and trichotillomania were classified in the same category in DSM-IV ('Impulse-control disorders not elsewhere specified') [10] further illustrates the underlying similarities between these disorders. Substance misuse and gambling are regarded as disorders characterised by impulsive/compulsive behaviours, with similar neural underpinnings to those identified in OCS disorders [11].

The biological bases of OCS disorders are incompletely understood. Following the finding that selective serotonin reuptake inhibitors (SSRI) are effective in the treatment of OCD and body dysmorphic disorder (BDD) in adults [12], the 'serotonin hypothesis' of OCS disorders gained popularity. Approximately 40-60% of patients respond to treatment with SSRIs [13], inferring, analogous to models of depression, that more than simply a serotonin 'deficit' is important in the neurobiology of OCS disorders. The cortico-striatal-thalamic-circuit (CSTC) – which comprises of glutamatergic, GABAergic and dopaminergic neurons [14] - has been implicated in the basic neurobiological model of OCD [15]. The striatum is considered to be involved in the initiation of behavioural responses and the acquisition of new habits [16]. Within the CSTC circuit there are two main pathways – the direct and indirect (Figure 1). The direct pathway works to disinhibit the thalamus, whereas stimulation of the indirect pathway increases inhibition of the thalamus [17]. Normal stimulation of the direct pathway causes fixation on a specific behaviour in response to a particular need until this need has been appeased. The indirect pathway works to suppress behaviours manifested driven by excitation of the direct pathway, allowing individuals to switch to a different behaviour [16]. In OCS disorders, the balance between direct and indirect pathways of the CSTC is considered to be disrupted, with the direct pathway having a disproportionately greater effect

over the indirect pathway [15]. This model posits that such imbalance may mediate OCS symptoms, with behaviours and cognitions that are usually held in check - such as the worries as following repetitive behaviours described in OCS disorders - instead being facilitated [18]. Evidence suggests that hyperactivity of the direct pathway may be correlated with symptom severity in OCD [19].

The role of oxidative stress has also been implicated in OCS disorders. Oxidative stress occurs when there is an imbalance of cellular oxidants and antioxidants, with high levels of oxidants causing toxicity and neuronal death [20] and is thought to contribute to the aetiology of psychiatric disorders [21]. Although there is little research focusing on OCS disorders more generally, there are data to indicate that oxidative stress may play an important role in OCD [22]. Oxidative stress, caused by decreased levels of antioxidants such as glutathione (GSH), has been implicated in OCD, where work has shown it to be related to the severity of symptoms [23]. Amelioration in OCD symptom severity, as measured by reduced Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, was found to be associated with decreased oxidative stress after twelve weeks of treatment with the SSRI fluoxetine 40mg/day [22]. The physiological correlates for this are not well understood at this time: the general finding of altered immune states is common to many mental illnesses [20], though arguments persist about sensitivity, specificity, and causality.

Treatment: current protocols and problematic efficacy

In the US, practice guidelines for the treatment of OCD advocate the use of both psychological and pharmacological interventions [24]. Psychological treatments are generally considered the most efficacious strategy, typically adopting Cognitive Behavioural Therapy (CBT) approaches. However waiting times for such interventions can be considerable, and

not all individuals improve with CBT, with data showing an improvement in target symptoms by more than 50% in just over half of OCD patients [2]. It is common for pharmacological interventions to be given whilst waiting for psychological treatment, in parallel to such work, or, in some cases depending on issues including patient choice and acceptability, instead of psychological work. SSRIs have been proven to be efficacious in the treatment of adults with OCD [24]. In children, due to concerns about SSRIs increasing suicidal thoughts, CBT is the first-line treatment for paediatric OCD, although SSRIs are recommended in addition to CBT for moderate to severe OCD [25].

To complicate matters, different studies use different criteria to determine whether or not people are treatment responsive [2]. There are many different axes along which severity of OCS symptoms can be measured, for instance time spent engaging in OCS behaviours, ability to resist urges, distress and impact on daily life: in clinical trials, change is generally measured by measures such as the Y-BOCS [26]. Typically, patients defined as ‘treatment responsive’ are defined as showing a 30-35% reduction in score, meaning that someone can be labelled as ‘treatment responsive’, but still be left with a number of time-consuming OCS symptoms which if one did not know of the previous reduction, could be classified as being in the mild-moderate range [3]. A systematic review comparing the efficacy of different treatments for TTM concluded that SSRIs were no more efficacious than placebo in reducing the severity of TTM symptoms [27]. Undoubtedly more efficacious pharmacological treatments for OCS disorders are needed to augment existing treatments.

N-acetyl-cysteine: Novel pharmacotherapeutics

N-acetyl-cysteine (NAC) is the acetyl derivative of cysteine which is quickly oxidised into cystine [28]. Although it has traditionally been used in the treatment of paracetamol overdose

and as a mucolytic agent, it has been postulated that NAC may exert a therapeutic effect on psychiatric and psychological disorders putatively caused – at least in part - by oxidative stress, such as schizophrenia and bipolar disorder; and those characterised by compulsive or impulsive symptoms, such as trichotillomania, onychophagia (pathological nail biting), gambling and substance misuse [11].

There are three potential mechanisms through which NAC might effect therapeutic change. Firstly, NAC is thought to decrease oxidative stress through the increased availability of cysteine, a rate-limiting substrate for cysteine-glutamate antiporters located on glial cells [28]. Cysteine-glutamate antiporters are considered key in governing the baseline levels of extrasynaptic glutamate [29] as well as in the feedback regulation of glutamate release [30]. A transient increase in levels of extrasynaptic glutamate seems to cause a subsequent decrease in its rate of release, through the stimulation of inhibitory metabotropic glutamate receptors on glutamatergic nerve terminals [31]. The increase in cystine levels after NAC administration thus allows alteration of the rate of exchange of glutamate and cysteine via the antiporters [28].

Secondly, cysteine is also a rate limiting substrate in the production of the antioxidant molecule GSH [32]. Within the cell, toxic by-products of glutamatergic neurotransmission and dysfunctional dopamine metabolism cause oxidative and nitrosative stress respectively [28]. Through the increased availability of GSH, which scavenges both of these toxic by-products, there is a lessening of oxidative and nitrosative stress, leading to decreased cell damage [28].

Finally, aside from influencing the glutamatergic system, NAC is also thought to modulate dopamine release. Recent evidence suggests glutamate regulation of dopaminergic activity in the ventral tegmental area of the brain [28], an area in which OCD patients have functional differences compared to healthy controls [33]. It has been proposed that there is increased dopamine neurotransmission in OCD sufferers [34]. When oxidised, dopamine forms hydrogen peroxide and free radicals [28] with dysregulation of dopamine signalling causing increased levels of neurotoxicity [35]. OCD has been associated with free radicals [36]. NAC relieves oxidative stress caused by neurotoxins following altered dopamine signalling, and lessens the reduction of dopamine transporters caused by previous high levels of dopamine release [37].

In the US, NAC is available in liquid, intravenous and oral forms. It is generally thought of as a relatively safe drug [3], with there being no prescription necessary to purchase the oral form. Mild side-effects such as headaches, rash and fever are thought to occur in approximately 1-5% of patients, while moderate side-effects such as hypertension, respiratory distress and increased blood pressure, occur in less than 1% of patients [38]. However, NAC is toxic in overdose and therefore it is of the highest importance that future studies investigate further its safety.

Aim

OCS disorders present considerable distress and suffering to those so afflicted and existing psychological and pharmacological treatments have limitations to their efficacy. Nascent data suggest that, as part of a putative oxidative-stress model, that OCS disorders might be amenable to amelioration by the anti-oxidative compound NAC. This work sets out to

systematically review the existing evidence on the efficacy of NAC as a treatment for OCS disorders.

METHOD

A systematic review of the efficacy of NAC on OCS disorders was carried out according to the PRISMA criteria [39]. Medline, Embase, and PsycINFO were searched via OvidSP while the Web of Science™ core collection was searched via Web of Science. Articles published in English were searched from inception until January 2014. The final search took place on the 1st July 2014 using the term ((obsessive OR compulsive) OR (skin AND picking) OR (body AND dysmorph*) OR hoarding OR trichotillomania OR glutamate*) AND (acetylcysteine)). Search terms were derived from the definition of OCS disorders according to DSM-5 [1].

Eligibility criteria:

Eligibility criteria were as follows.

Participants: Studies investigating adult and paediatric populations who manifested an OCS disorder as described by DSM-5 [1] were considered in the review.

Interventions: Studies were included if they investigated the therapeutic effect of NAC as either a stand-alone or adjunctive treatment for an OCS disorder.

Comparators: Where studies included a control group, intervention groups were compared groups taking a placebo.

Outcomes: Studies reporting behavioural outcome measures associated with OCS disorders, whether quantified by comprehensive measures e.g. Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [26] or Clinical Global Impression (CGI) [40] or described anecdotally were included.

Study design: Randomised control trials, retrospective case reports and case studies were included in the review.

Report characteristics: Reports published in English were included in the review.

RESULTS

Ten studies ultimately fulfilled the inclusion criteria (see Figure 2). Initially a total of 1007 records were identified by one of the authors (LS) after searching Medline, Embase, PsycINFO and Web of Science™ Core Collection. After removing duplicates, articles not in English and non-human studies a total of 618 records were left. The titles of these were screened and 59 records were identified as needing more thorough evaluation. The full texts of these articles were accessed and 49 were excluded, leaving ten studies to be included in synthesis. Of these: four were double-blind placebo-controlled trials; five were case studies; and one was a retrospective chart review. Three studies investigated cohorts of OCD patients; two investigated patients with TTM; two onychophagia; one dermatillomania; one described cases of TTM, dermatillomania and onychophagia; and one described cases of dermatillomania and TTM. All studies looked at adult populations except for two, [41, 42]

which investigated paediatric populations. For a full description of the studies and data extracted, see Table 1. Only one trial involved concurrent psychological intervention [41].

i) NAC and OCD

Three studies investigated the effect of NAC on OCD using various methodologies (one randomised placebo-controlled study, one retrospective chart review and one case study). Number of participants included in each study varied from only one to 48 with a follow-up period of 12-13 weeks.

Of the three studies investigating the effect of NAC on OCD, there was only one randomised, double-blind, placebo-controlled study [43]. In this 12 week study of 48 participants (mean age 30.93) half were randomised to the treatment group (NAC 600mg/day, doubled every week to a final dose of 2400mg/day), half to the placebo control group. Patients were recruited from two hospitals and had a primary diagnosis of OCD. Diagnoses were made by an experienced psychiatrist utilising DSM-IV [44]. Patients had failed to show a treatment response, defined as a Y-BOCS score of 15 or less, after 12 weeks of treatment with an SSRI. All participants continued on stable doses of medication during the study, and by the end of the twelve weeks 52.6% NAC patients had a full clinical response, defined as a 35% or greater reduction in Y-BOCS score, compared to 15% in the control group. However the rate of adverse events in the NAC group was notable, with eight patients reporting nausea/vomiting and four reporting mild diarrhoea. As a consequence of the adverse effects of NAC, three participants (12.5%) discontinued the study.

A retrospective chart review of 6 patients (mean age 48.8) with treatment resistant OCD with no control group was undertaken by Van Ameringen et al. [45]. Participants, who were all on SSRIs, were commenced on 500mg/day of NAC, increased to a maximum of 3000mg/day depending on tolerability and clinical response. Only one patient was found to have a therapeutic response to NAC over the intervention period of 12 weeks, defined by a 35% reduction in Y-BOCS score and a reduction of symptom severity as measured by the CGI scale [40] to 2.

The earliest study was a single case study documenting the symptoms of a 58 year-old female with childhood onset OCD, confirmed using a structured clinical interview [46]. NAC was administered for a total intervention period of 13-weeks alongside fluvoxamine 300mg/day. The initial dose was 600mg/day, but was titrated up to a total daily dose of 3000mg/day over the course of six weeks. There was a significant decrease in Y-BOCS score, and improvement in self-reported symptoms, which was maintained at a 2-month follow-up.

Taken together, the results of these three studies cautiously indicate the efficacy of NAC in the treatment of OCD. The most methodologically robust of these studies, the randomised, double-blind, placebo-controlled study carried out by Ashfar et al. [43] indicates significant difference in Y-BOCS and Clinical Global Impression-Severity Scale (CGI-S) score between the treatment and control group. However, the retrospective chart review (no randomisation, blinding or placebo-control) indicated a poor effect of NAC in the treatment of OCD. One strength of these findings is that each study has used a comprehensive scale upon which to base their findings as opposed to subjective measures such as self-report.

ii) *NAC and TTM*

Of the three studies investigating the effects of NAC on TTM, two were moderately sized double-blinded placebo-controlled RCTs (one conducted in an adult cohort and the other conducted in a paediatric cohort), and the final study was a case series. Studies ranged from including three participants to 50 participants, with a follow-up of 11 weeks to 7 months.

The most recent RCT was a twelve week trial [41] in a paediatric cohort (age range 8-17; n=39) randomised to NAC (n=20; dose titrated to a maximum of 2400mg/day over 4 weeks) and placebo (n=19). Participants had a primary diagnosis of TTM and were being treated with psychotherapy and stable medication (no addition, discontinuation or changes to dose in the 4 weeks prior to the trial). All subjects, regardless of intervention group, showed a statistically significant improvement in hair-pulling (measured by the Massachusetts General Hospital Hair-pulling Scale. (MGH-HPS) [47].

The other RCT [48] was conducted over 12 weeks in an adult cohort (n=50) with TTM randomised to NAC (n=25; dosed 1200mg/day for the first six weeks, thereafter increased to 2400mg/day) or the control group (n=25). All patients had a primary diagnosis of TTM as defined by DSM-IV [44]. Patients were included in the study if they had been taking a stable dose of medication for three months prior to the onset of the study and had no plans to change the dose during the study. Participants attending psychotherapy were also included in the study, as long as they had been attending for at least six months before the study. Participants in the treatment group showed a significant improvement compared to controls on both the severity subscale and the resistance and control subscale of the MGH-HPS ($p<0.001$ for both). 44% of the treatment group showed a 50% or greater reduction on the MGH-HPS compared to 0% of the control group. There was also a significant improvement shown on the Psychiatric Institute Trichotillomania Scale ($p=0.001$; PITS) [49] in the treatment as

compared to the control cohort. 56% NAC patients were ‘much’ or ‘very much’ improved at the trial’s conclusion, as measured by the CGI scale, whereas this was the case for only 16% of the control group.

The case series described three patients, one of whom suffered from TTM and onychophagia, another who suffered only from TTM and the last who suffered from dermatillomania [50]. Case 1 took 600mg/day NAC for 2 weeks, after which it was increased to 1200mg/day NAC, and at 5 weeks further increased to 1800mg/day and maintained for 4 weeks. No other psychotropic medication was being taken at this time. Over the intervention period, self-reported trichotillomania and nail biting symptoms had ceased. Case 2 had an initial dose of 600mg/day, increased to 1200mg/day after one week, and to 1800mg/day after three weeks, which was maintained for 4 weeks, before being increased once more to 2400mg/day for a duration of 7 months. Self-reported hair-pulling behaviour had completely ceased and the patient no longer needed to wear a wig. Case 3 started treatment with 600mg/day NAC for one week after which it was increased to 1200mg/day, maintained for 3 weeks, and then increased to 1800mg/day for 4 months. Self-reported picking behaviours completely ceased and only a mild urge to pick was reported.

Results from studies investigating the efficacy of NAC in TTM indicate that NAC may be efficacious in the treatment of TTM. Of the two RCTs carried out, one indicated a significant improvement in hair-pulling, as measured by the MGH-HPS, in the treatment condition but not the placebo condition [48]. The strength of this finding comes into question when considering results of the second RCT. Bloch et al. [41] found statistically significant decreases in hair-pulling, as measured by the MGH-HPS, in both the treatment and control group. Results from the case study series cautiously point toward the efficacy of NAC in the

treatment of OCS disorders, however all improvements are self-reported with no use of comprehensive rating scales.

iii) NAC and onychophagia

Two studies looked at the effect of NAC on nail-biting, one of which was a randomised, double-blind, placebo-controlled trial and the other of which was a case series. Number of participants ranged from three to 42 with a follow up duration of 2 months to 7 months.

The RCT was carried out on a paediatric cohort aged 6-18 [42], with 42 children randomised to either NAC (n=21; 200mg/day, increased 800mg/day over one week) or placebo (n=21). Participants were diagnosed according to DSM-IV criteria using the Farsi translation of the Kiddie Schedule for Affective Disorders and Schizophrenia [51]. The drop-out rate was high for both groups, leaving 14 in the NAC and 11 in the control group for final analysis. Nail-length increased significantly more in the NAC group at a 1-month follow-up ($p<0.04$; 5.21mm compared to 1.18mm in the control group); however, there was no statistically significant difference in nail-length at the 2-month follow-up.

NAC was found to have a therapeutic effect on nail-biting in a set of case studies documented by [52]. All three patients described in the study were being treated with NAC for bipolar disorder and experienced a subsequent alleviation of nail-biting behaviour. Case 1 took 2000mg/day NAC for 7 months, alongside lithium 900mg/day and quetiapine 300mg/day, with nail biting behaviour ceasing in the first two weeks. This amelioration continued for the entirety of the intervention period. Case 2 also took 2000mg/day NAC, this time for six months: after four months self-reported nail biting behaviour had ceased and was maintained

for the rest of the intervention period. Other medications being taken during the intervention period were 15mg/day mirtazapine, fish oil, zinc, magnesium, vitamin B6 and valerian. Case 3 took an unreported dose of NAC for 28 weeks, over which time there were self-reports of a reduction of nail-biting behaviour. No concurrent use of other medication was reported. Although this series was identified because participants were suffering from bipolar disorder, this study was not excluded from the review because pathological nail-biting is presently identified in DSM-5 under 'other specified obsessive-compulsive and related disorders' [1].

Together, these findings indicate that NAC may be an effective treatment for onychophagia, however strength of results is limited by the small sample sizes in both studies. The larger of the two studies randomised a total of 42 participants to treatment and placebo groups, but only reported results for 25 participants after a large number of participants dropped out of the study [42]. The strength of these findings of efficacy of NAC for onychophagia is also marred by the results indicating a statistically significant difference in nail-length between the treatment and control group only at the 1-month follow-up, with there being no statistical significant difference at the 2-month follow-up. The case series indicated only the cessation of self-reported nail-biting behaviour with no objective measurements available.

iv) NAC and dermatillomania

Two studies were found investigating the effect of NAC on dermatillomania, a case series and a case study. Number of participants ranged from one to three. Treatment and follow-up duration was unspecified in three of the four participants identified by these studies, but one follow-up duration is mentioned to be 10 months with a different participant shown to have a reduction in skin-picking behaviour for 1 year.

The case series of the treatment of NAC in skin-picking disorder described outcomes in three individuals [53]. Case 1 was diagnosed with a depressive episode, TTM and skin-picking. 1200mg/day NAC was taken over an unstated treatment period, alongside 75mg/day venlafaxine. During this period, self-reported skin-picking behaviour resolved and hair-pulling behaviour was described as improving partially. The patient then discontinued all medication resulting in a worsening of all symptoms. NAC was reinstated at a dose of 1800mg/day, as was venlafaxine at 75mg/day, after which there was again complete recovery from skin-picking behaviours and an improvement in hair-pulling behaviours. Case 2 developed skin-picking after having taken lithium 600mg/day and quetiapine 50mg/day for 1 month, though the reasons for being on such medications were not clearly stated. 1200mg/day NAC was introduced taken for 10 months, over which period self-reported skin-picking behaviour reduced. NAC was then discontinued and skin-picking behaviour was reinstated. After re-introducing NAC, skin-picking behaviour subsequently improved greatly. Case 3 took 1200mg/day NAC for an unstated period alongside fluoxetine 20mg/day as treatment for a moderate depressive episode, severe skin picking, pathological jealousy and an internet addiction. There was a substantial improvement in self-reported skin-picking behaviour.

A case study of a 24 year-old female treated with NAC for skin-picking disorder [54] was also identified. The participant also engaged in eight sessions of habit reversal therapy over the first weeks of the intervention period. Although neither the length of the intervention period nor the dose of NAC is stated, self-reports of skin-picking behaviour showed a reduced length of time spent engaging in the compulsive behaviour every day. This reduction in skin-picking behaviour was maintained for 1 year.

Results of studies investigating the efficacy of NAC in the treatment of dermatillomania indicate that NAC may have ameliorative effects on the presence of skin-picking behaviours. However, the strength of these studies is very weak, with there being no RCTs in the field. Results for the participants that are described here should be interpreted with caution, due to their small number and incomplete information on study duration and NAC treatment.

DISCUSSION

Despite the general dearth of information on the subject, our findings suggest there may be a potential efficacy of NAC in the treatment of OCS disorders as a stand-alone or adjuvant therapy, albeit much data are nascent and in methodologically less rigorous forms such as case series. In adult cohorts, randomised, placebo-controlled trials indicated the efficacy of NAC in combination with already stable psychotropic medication for the treatment of OCD [43] and TTM [48]. Case studies also indicated the efficacy of NAC as a stand-alone or adjunct treatment for OCD [46], TTM, excoriation and nail-biting disorder [50, 52-54]. However, a retrospective chart review indicated that NAC was not efficacious in the treatment of OCD [45]. Where comprehensive testing measures, such as the Y-BOCS [26], were used, some studies indicated a statistically significant improvement in measures of OCS disorders [43, 46, 48], whereas case studies described the amelioration of symptoms anecdotally [50, 52-54]. Both studies investigating paediatric cohorts were randomised, placebo-controlled trials which investigated the efficacy of NAC in combination with other stable psychotropic medication. NAC was found to be efficacious in the treatment of nail-

biting disorder after 1 months of treatment, although this therapeutic benefit was no longer visible after two months of treatment [42], and not found to be efficacious in TTM [41]. Adverse side effects were only reported in four studies [41-43, 50]. These ranged in severity, from mild flatulence [50] and nausea [43], to development of a full-body rash [41]. On the whole, drop-out rates were also low. Reasons for dropping out were linked to inability to comply with study demands [48] as well as adverse effects [41-43].

Previously, much neurobiological focus has been directed towards the serotonergic system, in no small part due to the therapeutic effect SSRIs can have on OCS behaviours. Medications targeting the glutamatergic system are in the early stages of research for their use in psychiatric disorders, such as OCS disorders.

High levels of oxidative stress, caused by decreased levels of glutathione has been shown to be correlated to the severity of symptoms of OCD [23]. NAC decreases oxidative stress by increasing the availability of cysteine, a rate-limiting substrate of cysteine-glutamate antiporters [28]. Cysteine-glutamate antiporters work to regulate extrasynaptic glutamate levels and are implicated in the feedback of glutamate release [11]. Increased rates of cysteine made available through the administration of NAC helps regulate extrasynaptic levels of glutamate. Glutamate regulation has recently been shown to affect dopamine transmission [28], which is also abnormal in OCD [33, 34].

The availability of cysteine is also a rate-limiting factor for the production of GSH [32]. The increased availability of cysteine following the administration of NAC therefore allows for the increased production of GSH. As GSH scavenges toxic by-products of oxidative and nitrosative stress, an increase in will result in decreased cell damage [28].

NAC has been shown to have clinical utility outside of OCS disorders, in the treatment of disorders of addiction, in which similar areas of the brain are implicated as those in OCS disorders [55, 56]. Seeing as drug addiction involves compulsive drug use [57] analogous to the compulsive behaviours seen in OCS disorders, this is perhaps unsurprising. Research into the treatment of drug addiction with NAC has shown promising results in reduction of drug use, cravings, withdrawal symptoms and relapse in cocaine [58, 59], marijuana [60] and nicotine addiction [61, 62]. NAC has also been shown to alleviate pathological gambling behaviour [63]. It has been hypothesised that NAC may be an effective treatment of anxiety disorders [11, 64], with which OCD was previously classified in DSM-IV-TR [10].

The results of this systematic review point cautiously towards the potential efficacy of NAC for the treatment of OCS disorders. Strengths of systematic reviews include the ability to collate all available evidence in order to clarify otherwise contradictory findings. In order to do this successfully, one must be mindful of the nature of the studies reviewed when interpreting results. Randomised, placebo-controlled trials were in the minority of the studies reviews, and even then, only two out of four studies demonstrated statistically significant differences between NAC and placebo treatment groups on comprehensive testing measures of the symptoms of OCS disorders [43, 48]. Of the remaining two studies, one showed statistically significant differences between the NAC and placebo treatment groups on nail-biting behaviour only at one-month follow-up, but these effects were no longer present at the two-month follow-up [42]. Bloch et al. [41] found no statistically significant difference between NAC and placebo treatment groups on a comprehensive measure of hair-pulling in paediatric TTM. A retrospective case review did not find any therapeutic effect of NAC on

OCD as measured by a comprehensive measure of OCD symptoms [45]. Case studies all indicated a therapeutic effect of NAC on OCS in adult cohorts.

One issue these studies face is the controversy in the diagnosis of OCS disorders. With the introduction of OCS disorders as a chapter in itself in DSM-5 [1] and the reclassification of some OCS disorders, there will likely be a period of confusion in the diagnosis of OCS disorders. This systematic review is further limited by language restrictions, with only English articles being reviewed. Due to the heterogeneity of the studies identified, it was not possible to conduct a meta-analysis to quantifiably determine the therapeutic effect of NAC on OCS disorders.

The number of randomised, placebo-controlled trials investigating the therapeutic effect of NAC on OCS disorders is very small, with further trials needed before a conclusive statement can be drawn regarding the efficacy of NAC in the treatment of such disorders. In an attempt to further understanding, three clinical trials are currently recruiting participants; two investigating OCD, one investigating a paediatric population (ClinicalTrials.gov: NCT01172275) and the other an adult population (ClinicalTrials.gov: NCT01555970), and one study investigating pathologic skin-picking (ClinicalTrials.gov: NCT01063348). This is a difficult area of research, with substantial difficulties when it comes to recruiting participants, resulting in the unfortunate termination of one recent clinical trial investigating NAC as a treatment for OCD in those for whom SRIs did not have a therapeutic effect (ClinicalTrials.gov: NCT00539513).

The clinical implications of this review are far reaching. Only 40-60% patients show a response to treatment with SSRIs [13], which are currently the first-line treatment for OCS

disorders such as OCD, BDD, TTM and excoriation disorder [12]. This leaves a high proportion of patients showing a less-than-optimal treatment-response to SSRIs, highlighting the importance of verifying the efficacy of other possible treatments for OCS disorders in order to optimise treatment. In those for whom SRIs do provide some amelioration, but not total cessation of symptoms, results indicate that NAC could be a useful adjuvant therapy.

As well as precipitating the amelioration of OCS symptoms, NAC seems to be well-tolerated, with few, mild adverse effects being caused. In addition to these features, NAC is also inexpensive and does not require a prescription [65], making it a very enticing option for the future treatment of OCS disorders. Placebo-controlled studies are lacking and more research is required to determine the guideline therapeutic dose, for both adults and children. Nevertheless, NAC has been shown to ameliorate behavioural compulsions manifested in OCS disorders. With clinical trials underway to further understanding, one can be cautiously optimistic about the promise of NAC as a treatment for OCS disorders.

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CONFLICT OF INTEREST STATEMENT

The Authors declare that there is no conflict of interest

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Figure 1. Figure showing the direct and indirect pathways within the CSTC.

CSTC = cortico-striatal-thalamic-circuit; GPe = globus pallidus externa; GPi = globus pallidus interna; STN = sub-thalamic nucleus; SNr = substantia nigra pars reticulata

Figure 2. Flow diagram showing study selection.

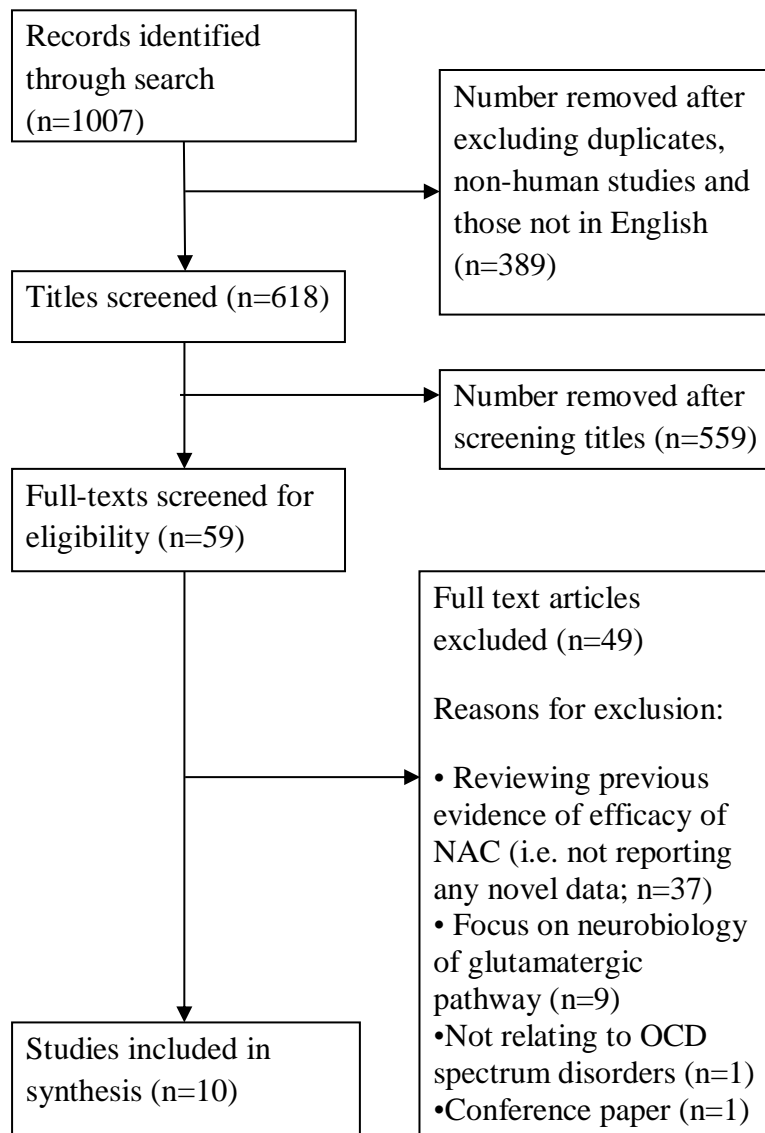


Figure 1

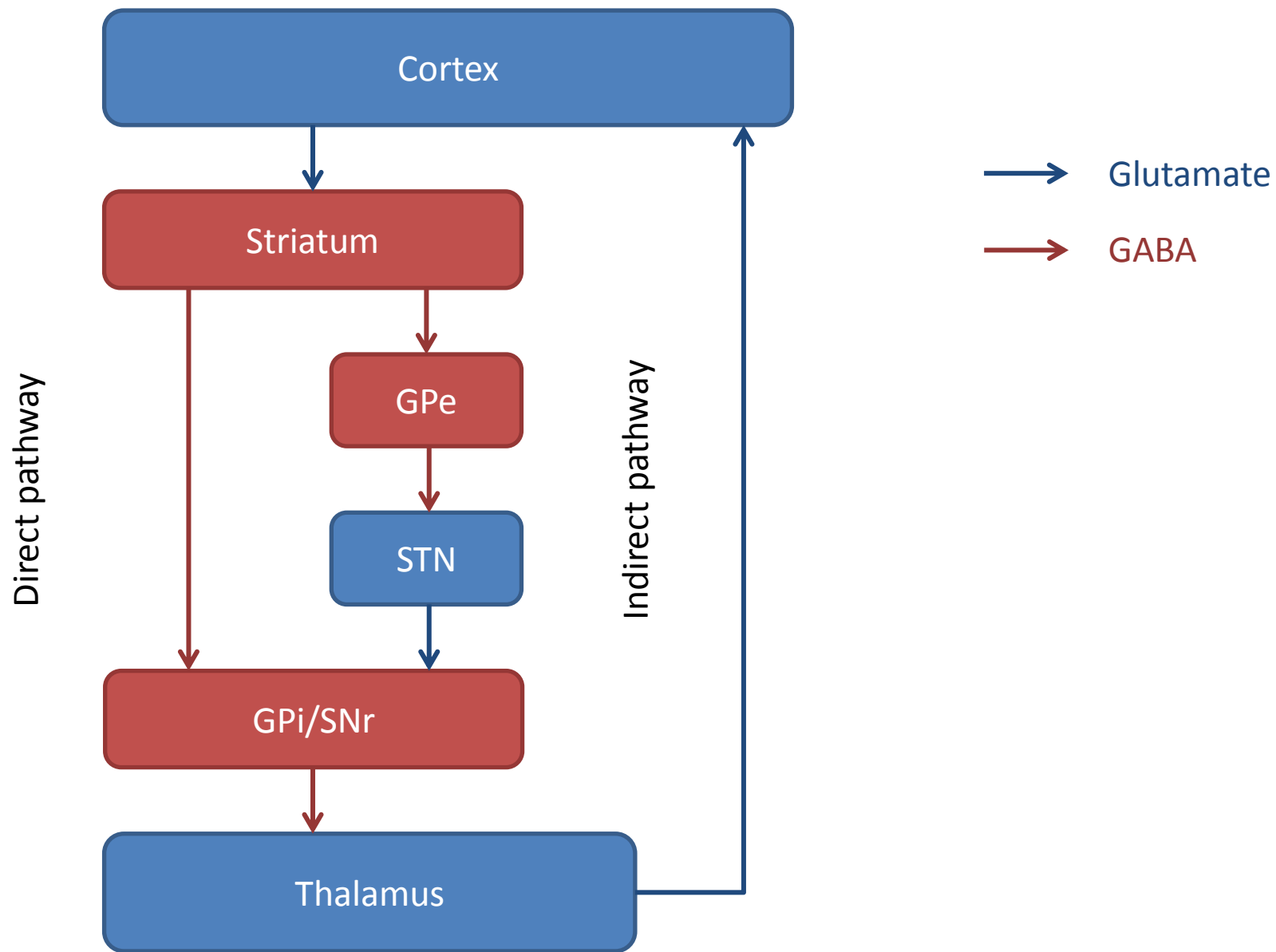


Table 1. OCS disorders as classified by DSM-5 and ICD-10.

DSM-5	Obsessive-compulsive disorder	ICD-10 Habit and impulse disorders	Somatoform disorders
Obsessive-Compulsive Disorder	Obsessive-compulsive disorder Predominantly obsessional thoughts or ruminations Predominantly compulsive acts [obsessional rituals] Mixed obsessional thoughts and acts		
Body Dysmorphic Disorder			Hypochondriacal disorder (includes body dysmorphic disorder)
Hoarding Disorder*			
Trichotillomania		Trichotillomania	
Excoriation Disorder*			
Substance/Medication-Induced Obsessive-Compulsive and Related Disorder*			
Obsessive-Compulsive and Related Disorder Due to Another Medical Condition*			
Other Specified Obsessive-Compulsive and Related Disorder	Other obsessive-compulsive disorders	Other habit and impulse disorders	
Unspecified Obsessive-Compulsive and Related Disorder	Obsessive-compulsive disorder, unspecified	Habit and impulse disorder, unspecified	

* Those that are only classified in DSM-5.

Table 2. The epidemiology of OCS disorders, licensed treatments and their efficacy.

Disorder	Prevalence	Typical age of onset, gender distribution (if available)	Licensed treatment(s) NICE Guidelines	Outcome data (if available)
OCD	1.6-2.3% adult population	Mean age of onset = 22-36. Males seem to develop OCD slightly earlier than females. Approximately 1:1 female:male.	First line – fluoxetine ^b , fluvoxamine, paroxetine, sertraline ^b , citalopram. Second line - clomipramine	Measurement: difference in Y-BOCS scores pre/post-test. Sertraline more efficacious than clomipramine; fluvoxamine as efficacious as clomipramine. Fluoxetine less efficacious than clomipramine. SSRIs and clomipramine show greater benefit vs placebo. Most improvement with clomipramine, then fluoxetine, fluvoxamine, sertraline.
Body dysmorphic disorder^a	0.5-1.1% adult population; 2.2% adolescent population	Usually begins in early adolescence. Approximately 1:1 female:male.	First line – fluoxetine. Second line - different SSRI (fluvoxamine, paroxetine, sertraline, citalopram) or clomipramine	SRIs often efficacious. Psychological therapies were more effective than pharmacotherapy. Fluoxetine significantly more effective than placebo
Hoarding disorder (included in OCD + BDD according to NICE guidelines)	2-5% adult population More prevalent in older than younger adults and children	Hoarding symptoms begin at average age of 12-13; interference with everyday functioning in mid-30s. Mixed findings; some studies	Treatment according to guidelines for OCD; hoarding symptoms rarely treated on their own	Relatively worse response to SSRIs compared with other OCD symptoms Hoarding symptoms reported to improve as much as other symptoms of OCD after paroxetine

		indicate higher prevalence in females, others indicate higher prevalence in males		
Trichotillomania (included in OCD + BDD according to NICE guidelines)	0.6-1% adolescents and young adult population 7 times more prevalent in adults than in children	Age of onset 10-13. Illness duration approximately 16-17 years. More common in females at all ages.	Treatment according to guidelines for OCD	Significant treatment effect favouring clomipramine vs control conditions. No difference between SSRI pharmacotherapy and control conditions SSRIs include fluoxetine, sertraline; TCAs include clomipramine, desipramine.
Excoriation disorder^a	1.4-5.4 in general adult population	Approximately 8:1 Female:male ratio, 8:1 (NB - may reflect differences in seeking treatment)	Treatment according to guidelines for OCD	SSRIs (fluoxetine, fluvoxamine, sertraline, paroxetine), doxepin, clomipramine, naltrexone, pimozide, olanzapine may be effective in reducing skin-picking

^a Those that differ between DSM-5 and ICD-10

^b Treatments licensed for children aged 8-18 in the UK

Table 3. Articles identified in systematic review; methodologies and findings.

Study	OCS disorder	Method of diagnosis	Comorbidities	Participants (number, mean age)	Study design	Dose (mg) and duration	Other concurrent pharmacological treatment	Other concurrent psychological treatment	Outcome measure	Findings	Dropout rate, adverse effects
Afshar et al. (2012) [41]	OCD	Diagnosis made by experienced psychiatrist based on DSM-IV	Not reported. Comorbidities diagnosed by experienced psychiatrist using DSM-IV	N=48. Mean age=30.93	Randomised, double-blind, placebo-controlled trial	Initial dose of 600mg/d. Doubled weekly to maximum dose of 2400mg/d (depending on individual tolerance and CGI-I score). 12 week intervention period.	SRI treatment continued throughout study at same dose as in pre-intervention phase	None. Patients undergoing psychotherapy or behavioural therapy were excluded from the study.	Y-BOCS, CGI-I scale, CGI-S scale	Significant difference in Y-BOCS score, CGI-S scale score between groups. No significant difference in CGI-I score between groups.	Mild-moderate nausea/vomiting, n=8. Mild diarrhoea, n=4. 3/24 participants in NAC condition dropped out due to adverse effects
Van Ameringen et al. (2013) [43]	OCD	Standardised initial assessment using Structured Clinical Interview for DSM-IV (SCID).	5/6 had comorbid conditions. ^a	N=6. Mean age=48.8 years.	Retrospective chart review	Initial dose of 500mg/d, increased to maximum dose of 3000mg/d, depending	Doses of concurrent OCD medication had been stable for at least 8 weeks ¹ .	Not reported	Y-BOCS, CGI scale.	Only 1/6 patients responded to NAC. Two patients reported worsening of	5/6 patients continued treatment for 12-week period. No adverse effects.

		Clinical interview with a psychiatrist to confirm diagnosis				g on clinical response and tolerability. Intervention period of up to 12 weeks.				symptoms.	
LaFleur et al. (2006) [44]	OCD	Diagnosis confirmed through Structured Clinical Interview.	History of recurrent major depression ; in remission for over 12 years.	N=1. 58 years old.	Case study	Initial dose of 600mg/d. Titrated to daily dose of 3000mg/d over period of 6 weeks and maintained for 7 weeks.	300mg/d fluvoxamine	No formal or manual-driven cognitive behavioural treatment plan	Y-BOCS. Self-reporting of intrusive thoughts.	Decrease in Y-BOCS score. Less disturbed by intrusive thoughts.	None reported
Bloch et al. (2013) [39]	TTM	Participants had a primary diagnosis of TTM.	Not reported.	N=39. Mean age; NAC=14.0, placebo=13.1	Randomised, double-blind, placebo-controlled, add-on trial	Initial dose of 600mg/d. After one week increased to 1200mg/d	All children on stable medication. Exact doses not reported.	Participants required to be on stable psychotherapy (over 3 months).	MGH-HPS	25% treatment responders (vs 21% placebo).	1 case of full-body rash which dissipated after NAC discontinued. Reported

						d. 12 weeks interventi on period.				No benefit if NAC as add-on for pediatric TTM.	missing a significant number of doses, NAC = 2; placebo = 1.
Grant et al. (2009) [46]	TTM	Patients met DSM-IV criteria for TTM, using physician - administe red TTM Diagnosti c Interview	28% reported symptoms consistent with major depressive disorder, 28% had an anxiety disorder, 36% had another impulse control disorder, 2% had an eating disorder	N=50. Mean age; NAC=35. 7, placebo=3 2.7	Randomi sed, double- blind, placebo- controlle d trial	1200mg/ d for 6 weeks, raised to 2400mg for last 6 weeks unless clinical improve ment.	56% patients taking psychotropi c medication. NAC group – 48%, placebo group – 64%. Medication required to be stable for 3 months	8% patients attending individual/ group psychother apy. All had been with the same therapist for at least 1 year (weekly attendance) .	MGH- HPS. PITS, CGI scale.	Significa nt improve ment in MGH- HPS, PITS and CGI scores in NAC group.	6 dropouts (88% completion) . 5 unable to comply with study schedule, 1 unrelated health concerns. No adverse effects in NAC group.
Odlaug & Grant (2007) [48]	Case 1=TT M and nail- biting.	Subjects underwen t structured clinical	Case 1, history of ADHD, diagnosed at age 5.	N=3. Case 1 age=28 Case 2 age=40. Case 3	Case study	Case 1= final dose 1800mg. Total interventi	Case 1 = no other psychotropi c medications	Case 1 = none reported. Case 2 = none	Self- reporti ng of skin- pickin	Case 1 = improve ment of skin- picking	Case 1 = Mild flatulence during first 2 weeks.

	Case 2=TT M. Case 3=skin - pickin g. NB – 5 patient s enrolle d in study, only those who respon ded were presen ted.	interview s.	Case 2, not reported. Case 3, no comorbidi ties, but history consistent with bulimia nervosa.	age=52.		on period of approxi mately 7 months. Case 2= final dose 2400mg/ d. Total interventi on period of approxi mately 8 months. Case 3= final dose 1800mg/ d. Total interventi on period of approxi mately 6 months.	. Case 2 = none reported. Case 3= none reported.	concurrent with NAC treatment. Case 3 = none concurrent with NAC treatment.	g and hair-pulling behavi our.	and hair-pulling behaviou r. Case 2 = complete abstinence from and cessation of urges to pull hair. Case 3 = complete absence of picking behaviou r, with occasion al urges.	Case 2 = none experience d. Case 3= none reported.
Ghaniza deh et al. (2013) [40]	Nail-biting	Diagnosis made according to DSM-IV diagnosti c criteria	. NAC group, n=10. Placebo group, n=9 ^b .	N=42. Mean age NAC=9.2 8, placebo=1 0.76.	Randomi sed, double-blind, placebo-controlle d trial	Initial dose of 200mg/d. Increased to 800mg/d over	NAC group – 9/14 children taking other medication ^b . Placebo group –	Participant s were excluded if they were participatin g in any psychologi	Increas ed nail length.	Significa nt increase only in NAC group at 1 month.	NAC group, dropped out due to adverse effects, n=2.

		using the Farsi Translati on of the Kiddie Schedule for Affective Disorders and Schizoph renia and physical examinati on.				course of a week Total interventi on period of 2 months.	11/11 ^b .	cal therapy for nail-biting.		(No differenc e at 2 months)	
Berk et al. (2009) [50]	Nail-biting	No formal diagnosis of nail-biting reported	All diagnosed with bipolar disorder. Case 1 = other diagnosed comorbidi ties. Cases 2 and 3 = symptoms of other psycholog ical disorders ^c	N=3. Case 1 age=46. Case 2 age=44. Case 3 age=46.	Case study	Case 1=2000m g/d, 7 months. Case 2=2000m g/d, 4 months. Case 3=2000m g/d, 7 months.	Case 1=900mg lithium, 300mg quetiapine. Case 2=15mg mirtazapine.	None reported	Self-reports of nail-biting behavi our.	Stopping of nail-biting.	None reported

Grant et al. (2012) [52]	Skin-picking disorder	Meets the proposed diagnosis for skin-picking disorder	None reported	N=1. 24 years old.	Case study	Dose not reported. Duration of 1 year.	None reported	8 sessions of habit reversal therapy over several weeks	Self-report of skin-picking behaviour	Skin picking behaviour reduced from 2-3 hours to 5-10 minutes daily	None reported
Silva-Netto et al. (2014) [51]	Case 1 = skin-picking disorder and TTM Case 2 = skin picking disorder Case 3 = skin picking disorder	Not reported	Case 1 = depressive episode, TTM. Case 2 = symptoms of mania. Case 3 = moderate depressive episode, pathological jealousy, internet addiction.	N=3. Case 1 age = 45. Case 2 = 40. Case 3 = 31.	Case study	Case 1 = final dose of 1800mg/d. Exact durations not reported. Case 2 = final dose of 1200mg/d. Exact durations not reported. Case 3 = 1200mg/d. Exact durations not reported.	Case 1 = 75mg/d venlafaxine. Discontinued then reinstated at same dose. Case 2 = 600mg/d lithium, 50mg/d quetiapine. Case 3 = 20mg/d fluoxetine	Case 1 = none reporter. Case 2 = none reporter. Case 3 = later referred elsewhere for psychotherapy.	Self-reports of TTM and skin picking behaviour.	Case 1 – TTM improved partially, skin picking resolved completely. Case 2 – cessation of skin picking. Case 3 – substantial improvement in skin picking	None reported

Abbreviations: NAC = n-acetylcysteine. SRI = serotonin reuptake inhibitor. OCD = obsessive-compulsive disorder. TTM = trichotillomania. ADHD = Attention Deficit Hyperactivity Disorder. Y-BOCS = Yale–Brown Obsessive Compulsive Scale. CGI = Clinical Global Impression; CGI-I = Clinical Global Impression –Improvement; CGI-S = Clinical Global Impression –Severity. MGH-HPS = Massachusetts General Hospital Hair-pulling Scale. PITS = Psychiatric Institute Trichotillomania Scale. Mg/d = milligrams per day.

^{a, b, c} = See full-text article for details.

Table 4. Methodology and quality of articles included in review

Study	OCS disorder	Number of participants	Study design	Blinding	Outcome measure	Duration of follow-up	Confounders	Quality of study (as defined by the GRADE approach [53])	Comments
Afshar et al. (2012) [41]	OCD	N=48	Randomised, double-blind, placebo-controlled trial	Investigators blinded to the drugs used. Researchers involved in allocation to treatment/placebo group had no role in treatment or collection of data	Y-BOCS, CGI-I scale, CGI-S scale	12 weeks. Patients were assessed at 4 weeks and 12 weeks.	No systematic way of increasing dose of NAC to maximum. No report of individual final dose of participants. Comorbidities. Other pharmacological treatments	Moderate	Larger sample size, more rigorous methodology and objective rating scale. Blinding of the sample not great. No report of inter-rater reliability.
Van Ameringen et al. (2013) [43]	OCD	N=6	Retrospective chart review	No blinding	Y-BOCS, CGI scale.	12 weeks	No systematic administration of NAC across patients. All patients were taking other psychotropic medication. 5/6 patients had a comorbid disorder. Not	Low	Small sample size, no randomisation/placebo-control/blinding (due to nature of study), objective rating scale

							reported whether patients were undergoing concurrent psychological therapy.		
LaFleur et al. (2006) [44]	OCD	N=1	Case study	No blinding	Y-BOCS. Self-reporting of intrusive thoughts.	2 months	Taking fluvoxamine, History of major depressive disorder. No objective measure of improvement of symptoms.	Very low	Very small sample size, no randomisation/placebo-control/blinding (due to nature of study), objective rating scale
Bloch et al. (2013) [39]	TTM	N=39	Randomised, double-blind, placebo-controlled, add-on trial	Subjects, parents, investigators, those performing assessments were blinded	MGH-HPS	12 weeks	For inclusion, participants required to be on stable pharmacotherapy and stable psychotherapy (3 months prior to study). Exact details of patients' pharmacotherapy and psychotherapy not reported.	Moderate	Larger sample size, more rigorous methodology and objective rating scale

Grant et al. (2009) [46]	TTM	N=50	Randomised, double-blind, placebo-controlled trial	Double blinding	MGH-HPS, PITS, CGI scale.	12 weeks	56% patients taking concurrent psychotropic medication; 8% patients had concurrent psychotherapy. 60% patients had at least one clinically important comorbidity. 72% of patients in the treatment group received a dose increase after 6 weeks of the study duration (vs 88% placebo group).	Moderate	Larger sample size, more rigorous methodology and objective rating scale
Odlaug & Grant (2007) [48]	Case 1=TTM and nail-biting. Case 2=TTM. Case 3=skin-	N=3	Case study	No blinding	Self-reporting of skin-picking and hair-pulling behaviour.	Case 1 – 4 months. Case 2 – 5 months. Case 3 – 4 months.	Patients had comorbidities. No systematic administration of NAC across patients. No objective measure of improvement of symptoms.	Very low	Small sample size, no randomisation/placebo-control/blinding (due to nature of study), subjective rating scale

	picking disorder								
Ghanizadeh et al. (2013) [40]	Nail-biting	N=42	Randomised, double-blind, placebo-controlled trial	Researcher who measured nail length and patients was blind to group allocation	Increased nail length.	1 month	Patients had comorbidities ^a . Patients taking concurrent psychotropic medication. No report of individual final dose of participants. High withdrawal rate from study.	Moderate	Larger sample size, more rigorous methodology and objective rating scale
Berk et al. (2009) [50]	Nail-biting	N=3	Case study	No blinding	Self-reports of nail-biting behaviour.	Case 1 – 7 months. Case 2 – 2 months. Case 3 – 28 weeks	Patients had comorbidities and were taking concurrent psychotropic medication. No systematic administration of NAC across patients. No objective measure of improvement of symptoms.	Very low	Small sample size, no randomisation/placebo-control/blinding (due to nature of study), subjective rating scale

Grant et al. (2012) [52]	Skin-picking disorder	N=1	Case study	No blinding	Self-report of skin-picking behaviour	1 year	No report of any comorbidities or other therapy (pharmacotherapy or psychotherapy) reported. No objective measure of improvement of symptoms.	Very low	Very small sample size, no randomisation/placebo-control/blinding (due to nature of study), subjective rating scale
Silva-Netto et al. (2014) [51]	Case 1 = skin-picking disorder and TTM Case 2 = skin-picking disorder Case 3 = skin-picking disorder	N=3	Case study	No blinding	Self-reports of skin-picking and hair-pulling behaviour	Case 1 – not reporter. Case 2 – over 10 months, not specified. Case 3 – not reported.	Patients had comorbidities and were taking other psychotropic medication. No mention of psychotherapy. No systematic administration of NAC across patients. No objective measure of improvement of symptoms.	Very low	Small sample size, no randomisation/placebo-control/blinding (due to nature of study), subjective rating scale

Abbreviations: NAC = n-acetylcysteine. OCD = obsessive-compulsive disorder. TTM = trichotillomania. Y-BOCS = Yale–Brown Obsessive Compulsive Scale. CGI = Clinical Global Impression; CGI-I = Clinical Global Impression –Improvement; CGI-S = Clinical Global Impression – Severity. MGH-HPS = Massachusetts General Hospital Hair-pulling Scale. PITS = Psychiatric Institute Trichotillomania Scale.

^a= See full-text article for details of comorbidities.